R E V I E W

Systemic Lupus Erythematosus Management in Pregnancy

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Abstract: Systemic lupus erythematosus (SLE) affects reproductive aged women. Issues regarding family planning are an important part of SLE patient care. Women with SLE can flare during pregnancy, in particular those who have active disease at conception or prior history of renal disease. These flares can lead to increased adverse pregnancy outcomes including fetal loss, pre-eclampsia, preterm birth and small for gestational aged infants. In addition, women with antiphospholipid antibodies can have thrombosis during pregnancy or higher rates of fetal loss. Women who have anti-Ro/SSA and anti-La/SSB antibodies need special monitoring as their offspring are at risk for congenital complete heart block and neonatal lupus. Ideally, SLE patients should have their disease under good control on medications compatible with pregnancy prior to conception. All patients with SLE should remain on hydroxychloroquine unless contraindicated. We recommend the addition of 81mg/d of aspirin at the end of the first trimester to reduce the risk of pre-eclampsia. The immunosuppressive azathioprine, tacrolimus and cyclosporine are compatible with pregnancy and lactation, mycophenolate mofetil (MMF)/mycophenolic acid are not. Providers should use glucocorticoids at the lowest possible dose. Methotrexate, leflunomide and cyclophosphamide are contraindicated in pregnancy and lactation. SLE patients on the biologics rituximab, belimumab and abatacept can continue these medications until conception and resume during lactation.

Keywords: systemic lupus erythematosus, fertility, pregnancy, medications

Introduction

Systemic lupus erythematosus (SLE) is a multi-organ system disorder that predominantly affects reproductive aged women. As such, issues regarding fertility and pregnancy are an important part of SLE patient care. SLE pregnancies are associated with increased incidence of disease flares as well as adverse pregnancy outcomes (Table 1). Previously, these factors combined with limited knowledge regarding medication compatibility with pregnancy led many clinicians to dissuade their SLE patients from pursuing pregnancy. However, over the past several decades, a better understanding of SLE disease course and management during pregnancy has improved maternal and fetal outcomes. In this review, we will discuss SLE management during conception, through pregnancy and the post-partum period.

Overview of SLE

SLE is a chronic disease characterized by autoreactive T and B cells leading to pathogenic autoantibodies and immune complex deposition resulting in tissue damage.[1] Diagnosing SLE can be challenging as the disease often develops slowly and evolves over time.[2] Moreover, many organ symptoms can be involved including the skin, the musculoskeletal, pulmonary, cardiovascular, hematologic, renal and nervous systems. The vast majority of patients will have a positive anti-nuclear antibody and often have other autoantibodies. Diagnosis requires the presence of an ANA, and the presence of other autoantibodies and/or clinical manifestations.[3] Epidemiologic studies estimate the prevalence of SLE is between 45.2 and 102.9 per 100,000 with an incidence of 2.4–7.2 per 100,000/year.[4,5] The highest incidence of SLE is seen in women, peaking during their reproductive years with a female to male prevalence ratio of 7–9:1.[6,7] The X chromosome and sex hormones may be responsible for the uptick in incidence among women as these have been associated with immune dysregulation. Candidate risk genes for SLE have been

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Table 1 Study Findings in SLE Pregnancy

Key Points	References	Study Findings
SLE increases APO	[25]	SLE increases hospital stay, HTN, IUGR, and C sections
	[26]	SLE increase risk for preeclampsia, maternal death, infection and thrombosis during pregnancy
	[38]	SLE increase risk for IUGR, preterm birth and stillbirth
Predictors of APO	[18]	History of lupus nephritis and high disease activity predicts adverse maternal outcomes
	[20]	PROMISSE study: Predictors of APO include: maternal flares, higher disease activity, lower increases in C3, presence of LAC.
	[24]	Type of organ-system active in prior 6 months before pregnancy, predicted type of pregnancy disease flare pregnancy
	[39]	SLE flares, HTN, and Raynaud's predicts IUGR
	[47, 48]	Moderate - high titers of aPL (IgG/IgM), LAC predicts fetal loss and poor maternal outcomes
Control SLE disease for 6 months prior to pregnancy	[19]	Active lupus at time of conception were associated with renal and hematologic flares
	[28]	Active disease was associated with increased risk for preeclampsia and preterm births
	[29]	Preterm labor were more common with active lupus nephritis
	[9, 33, 36, 37]	Pregnancy loss is higher in those with active disease 6 months prior to conception
HCQ reduces risk of APO	[21, 22]	HCQ reduces risk of flares during the pregnancy and postpartum periods
	[23]	HCQ reduces risk of preeclampsia

Abbreviations: aPL, antiphospholipid antibodies; APO, adverse pregnancy outcomes; HCQ, hydroxychloroquine; IUGR, intrauterine growth retardation; HTN, hypertension; LAC, lupus anticoagulant; SLE, systemic lupus erythematosus.

discovered on the X chromosome (eg, Foxp3, TLR7, IRAK1, and CD40 ligand), and estrogens have effects on B cell maturation, antibody production, Th2 responses, and survival of autoreactive cells.[7] Thus, it is not surprising that pregnancy can impact SLE disease activity, and conversely SLE can impact pregnancy outcomes.

Reproductive Potential

SLE affects fecundity (probability of conception/reproduction) and fertility (reproductive capacity). Several factors impact the number of offspring in patients with SLE, including active inflammatory disease, comorbidities (eg, renal insufficiency, lupus nephritis, and anti-phospholipid syndrome), exposure to gonadotoxic treatments, advanced maternal age, psychosocial aspects and pregnancy loss (discussed below).[8–10] Lupus activity, even mild, can cause oophoritis and interrupt the hypothalamic pituitary ovarian axis.[11] Flares also have been associated with hyperprolactinemia, affecting the ovulation process.[12] Patients may present with amenorrhea and menstrual irregularity. Pasoto et al reported 53% of SLE patients under 40 years of age had menstrual alterations, and patients with high disease activity were more likely to endorse irregular menses.[13] Anti-Mullerian hormone (AMH) levels and antral follicular count (AFC) are predictors of ovarian reserve; a reduction in levels may indicate impaired fertility. Cohort studies have found AMH and AFC levels in SLE patients were significantly lower compared to age-matched healthy controls even in those with normal menstruation.[13,14]

Cyclophosphamide (CYC) is an alkylating agent used in the treatment of severe manifestations of SLE (eg, class III/ IV lupus nephritis, severe neurological inflammation, pulmonary alveolitis/hemorrhage). This medication can directly damage oocytes,[15] however, gonadotropin-releasing hormone agonists can mitigate this toxicity.[16] Women previously treated with CYC experienced greater rates of amenorrhea and early menopause. Ovarian insufficiency is more likely with age (over 30) and cumulative doses greater than 10 grams.[17]

Disease Activity During Pregnancy

Several studies have shown that active disease at the time of conception correlates with disease flares during pregnancy. A study of 55 pregnancies in 39 women with SLE recorded clinical and laboratory data regularly six months prior to pregnancy through the first year post-partum. In this study, history of nephritis and high disease activity, as measured by the SLE Disease Activity Index (SLEDAI), predicted adverse maternal outcome during pregnancy.[18] In another study of 155 patients with lupus who became pregnant, active lupus at the time of conception was associated with renal and hematologic flares. In this cohort, 6.1% of women with active disease during pregnancy died and 15.9% developed organ failure; in addition, hypocomplementemia and anti-dsDNA at the time of conception were also associated with disease flares.[19] In the prospective study, Predictors of Pregnancy Outcome: Biomarkers in Antiphospholipid Antibody Syndrome and Systemic Lupus Erythematosus (PROMISSE), fewer than 10% of 318 patients with mild –moderate disease during the first trimester of pregnancy had mild flares and only 3% had severe flares.[20] Several studies have shown that continuation of hydroxychloroquine during pregnancy reduces the risk of flare during pregnancy and in the post-partum period.[21,22] Moreover, in a study of 316 lupus pregnancies, hydroxychloroquine reduced the risk of preeclampsia.[23]

Not only does disease activity in the six months preceding conception predict flare, but also the type of organ involvement in the pre-conception period predicts the type of disease flare during pregnancy. Tedeschi et al showed that the organ-system that was active in the six months prior to conception predicted the organ system involved in a pregnancy disease flare. Thus, women with hematologic manifestations prior to conception tended to have hematologic manifestations during pregnancy.[24]

Pregnancy Outcomes

Women with SLE have more adverse pregnancy outcomes than control women. In a study of the nationwide inpatient sample that included 4000 SLE pregnancies, lupus pregnancies had longer hospital lengths of stay, increased hypertension, higher rates of intrauterine growth restriction (IUGR) and C-section rate.[25] The latter finding is driven by both provider and patient preference and may not reflect a medical indication. In a subsequent study using the same database but expanded years, there was a three-fold increased risk of pre-eclampsia, a 20-fold increase in maternal death, and increased rate of infections and thrombosis among SLE patients.[26] More recent data has shown improvement in maternal mortality and fetal death rates, although rates are still higher than in the control population. The incidence of cesarean section rates and pre-eclampsia continues to remain higher in SLE pregnancies and have not significantly changed over time.[27] In the aforementioned PROMISSE study, 19% of patients had adverse pregnancy outcomes including fetal loss after 12 weeks, neonatal death, preterm delivery and small for gestational aged infants. Baseline predictors include the presence of a lupus anticoagulant (OR 8.32, 95% CI 3.59–19.26), antihypertensive use (OR 7.05, 95% CI: 3.05–16.31), physician global assessment >1 (OR 4.02, 95% CI 1.84–8.82), thrombocytopenia (OR 1.33 per 50K decrease, 95% CI 1.09–1.63), maternal flares, higher disease activity and lower increases in C3 later in pregnancy.[20] The Medical Birth Registry of Norway reported outcomes of births in women with SLE and concluded active disease was associated with increased risk for preeclampsia (OR 5.33 compared to population controls, OR 3.38 compared to inactive disease) and preterm births (OR 8.66 compared to population controls, OR 3.36 compared to inactive disease.[28] A study of maternal and fetal outcomes over 3 decades by the Mayo clinic found that patients with active lupus nephritis compared to those who had quiescent disease had higher incidence of maternal complications (57% vs 11%, p < 0.001). Women with active nephritis were more likely to deliver preterm (median 34 weeks vs 40 weeks p = 0.002) and to have fetal loss (35% vs 9%, p = 0.031).[29]

Preeclampsia versus Lupus Flare

One of the most challenging clinical conundrums is differentiating SLE flare from pre-eclampsia. This is particularly so because up to 20% of lupus pregnancies are complicated by pre-eclampsia. This differentiation is not merely academic as pre-eclampsia is treated with immediate delivery whereas lupus flare is managed with immunosuppression. While both conditions can present with hypertension and proteinuria, urinalysis in pre-eclampsia is less likely to reveal an active sediment than in SLE flare. Thrombocytopenia is common to both but elevations of liver function tests are more suggestive of pre-eclampsia. In lupus flares, lower white blood cell counts, complement levels, and uric acid are seen than in pre-eclampsia.[30,31] (Table 2)

Fetal Outcomes

Fetal Loss

Previously, fetal loss in SLE pregnancies was as high as 43%. This rate declined to 17% in 2002.[32,33] In a cross-sectional study of 356 SLE pregnancies, SLE pregnancies were more than twice as likely to end in fetal death than non-SLE pregnancies.[34,] Another study of 148 lupus pregnancies compared to 78,905 non-lupus pregnancies found the rate of stillbirth was higher with lupus (OR 4.84 [CI, 1.72,11.08]) and associated with severe maternal disease).[35] Risk factors for pregnancy loss include: the presence of antiphospholipid antibodies (aPL), lupus nephritis, renal insufficiency, and increased lupus activity in the 6 months preceding or during pregnancy.[9,33,36,37]

Fetal Complications

One study from Taiwan of 2059 SLE offspring reported higher rates of intrauterine growth restriction, preterm birth and stillbirth.[38] Similarly, an Italian group reported higher risk of preterm delivery and small for gestational aged infants in their SLE cohort.[39] This group also found SLE pregnancies were more likely to end in preterm delivery, particularly in patients with a history of lupus nephritis and hypertension. Intrauterine growth restriction was associated with hypertension, Raynaud's, and disease flares.

Neonatal Lupus

Approximately one-third of women with SLE will have anti-Ro/SSA and anti-La/SSB antibodies. In 10% of offspring of pregnant women with these antibodies, neonatal lupus can occur (NL). Neonatal lupus consists of cutaneous or cardiac manifestations. In cutaneous neonatal lupus, the infant has a photosensitive rash and can have elevated liver function tests. These findings disappear after six months of life. In 1–2% fetuses of mothers with anti-Ro and anti-La antibodies, congenital complete heart block (CCHB) can occur. This incidence increases to 17% if the mother has had a previous child with CCHB.[40] Congenital complete heart block can lead to fetal death in 17.5% of affected fetuses most occurring before the 30th week of gestation. While no formal guidelines exist for monitoring for the development of heart block, professional societies recommend serial fetal echocardiography between 16 weeks and 26 weeks of gestation.[41] Data

Table 2 Differentiating SLE Flare from Pre-Eclampsia

	SLE Flare	Pre-Eclampsia
Hypertension	+	+++
Proteinuria	+	+++
Active urine sediment	+++	-
Wbc	Low-normal	High (secondary to pregnancy)
Platelets	Low-normal	Low
LFTs	Normal	Elevated
Complements	Low	Normal or high
Uric Acid	Low	Normal or high

suggest hydroxychloroquine administration during pregnancy in anti-Ro and anti-La positive mothers can reduce the reoccurrence rate of CCHB.[42]

Long–Term Outcome

The literature regarding long-term outcome of children of women with lupus is conflicting with some groups reporting increased usage of special educational services by children born to mothers with SLE and aPLs[43] while others found that while maternal SLE is a risk factor for pre-term birth it is not a risk factor for neurological disease in children born to SLE mothers.[44]

Management

Patients with SLE can and do have successful pregnancies. Pregnancy outcomes are better when there is planning and close monitoring of the patient during this process.The American College of Rheumatology (ACR) published evidence-based guidelines detailing a roadmap to optimize maternal and fetal outcomes in patients with rheumatic diseases.[41] A multidisciplinary team approach with close rheumatologic, obstetric, and neonatal monitoring is important from preconception to parturition. Box 1 lists good clinical practices (GCPs) for pregnancy planning for patients with SLE.

Pre-Pregnancy Screening and Contraception

A planned pregnancy is important to allow time to optimize treatment and tighten disease control. End-organ damage may be a contraindication to pregnancy; examples include severe pulmonary hypertension, pulmonary fibrosis, cardiomyopathy, valvular dysfunction, severe renal insufficiency, or end stage renal disease, history of major strokes or catastrophic antiphospholipid syndrome.[45,46] Patients with these conditions should avoid pregnancy. Additionally, pre-conceptual counseling will reduce risk of exposure to teratogenic medications, disease flares, and adverse pregnancy outcomes (APOs). An important part of pre-conception counseling is to ascertain the patient's pregnancy plans. One easy way to incorporate this into clinical practice is to ask "Would you like to become pregnant in the next year?."[47] If the patient wants to avoid pregnancy, refer the patient for effective Contraception.

Preconceptual Risk Assessment

In patients desiring pregnancy, remission or low lupus disease activity state (LLDAS) is the goal before pregnancy is attempted. Active disease status will increase the risk of poor outcomes to mother and baby. Hence, to minimize risk for APOs, patients should be in LLDAS or remission for 6 months before trying to conceive on medications compatible with pregnancy. Those with moderate or severe disease activity should delay pregnancy until the disease is controlled on stable, pregnancy-compatible medications.

Box 1 Preconception Counseling: The Checklist

Ask the One Key Question: "Do you plan to get pregnant in the next year?"

Discuss birth control with patients who do not desire pregnancy

Ensure SLE disease control for at least 6 months (if still with moderate to severe disease, delay pregnancy and discuss birth control)

Evaluate if the patient on pregnancy compatible medications

Evaluate for the presence of anti-Ro/SSA, anti-La/SSB antibodies, or antiphospholipid antibodies and the lupus anticoagulant

Assess if comorbidities are controlled (eg, diabetes, hypertension, renal disease)

Assemble a team (eg, maternal fetal medicine, rheumatologist, neonatologist/pediatric cardiologist, and nephrologist, if applicable)

Biomarkers Predictive of Pregnancy Outcomes

Women with SLE anticipating pregnancy should be tested for the presence of anti-Ro/SSA, anti-La/SSB and antiphospholipid antibodies (eg, anticardiolipin IgG and IgM, b2-glycoprotein-I IgG and IgM, and the lupus anticoagulant (LAC)); these antibodies portend serious complications during pregnancy. Moderate and high titers of antiphospholipid antibodies in combination with the LAC confers the highest risk for poor fetal and maternal outcomes.[47,49]

Pregnancy Monitoring

Lupus pregnancies are high-risk pregnancies. A collaborative approach to monitoring the pregnant patient is essential; the team should comprise a rheumatologist, maternal fetal medicine specialist (also known as "high-risk OB"), and if applicable, a nephrologist and pediatric cardiologist. The patient should have regular assessments during pregnancy to identify potential complications and receive early intervention. Physiological pregnancy changes may resemble SLE disease activity, including arthralgias, fatigue, rashes, and swelling. Laboratory changes also occur during a healthy pregnancy. Distinguishing which changes are physiological versus pathological may be difficult, but understanding normal pregnancy physiology is essential.

Pregnancy will cause significant anatomical and physiological transformations affecting every organ system.[50] Plasma volume expands by 50% and is proportional to the baby's birthweight. With the expansion of volume cardiac output will increase by 40% during normal pregnancy Cardiac murmurs will be more evident and peripheral edema and pulmonary edema can occur. Renal changes also result from increased blood flow. A pregnant woman's glomerular filtration rate (GFR) is increased by 50–85%.[51] This in turn increases the fractional excretion of protein and uric acid.

Hemoglobin and platelet levels decrease in a normal pregnancy, while the erythrocyte sedimentation rate (ESR) increases. A study of more than 1000 healthy pregnant women found the ESR doubles in the second half of pregnancy from 18–48 mm/h to 30–70 mm/h; gestational age along with hemoglobin concentration will affect ESR levels.[52] In contrast, C-reactive protein (CRP) levels do not rise during pregnancy; if elevated, this more likely indicates disease flare or infection. Hypercoagulability occurs in normal pregnancy; this is related to an increase of factor VIII, IX, X and fibrinogen; however, concentrations of anticoagulants, anti-thrombin and protein S are decreased contributing to thrombosis risk. This hypercoagulable state will persist from the first trimester to at least 6–12 weeks following parturition.[50] Additionally, complements will rise in a healthy pregnancy; they are important in host defenses against infection and for clearing apoptotic and necrotic cells. Elevated levels of C4, C3 and activation products C4d, C3a, and SC5b-9 are common in pregnancy; however, dysregulation of the complement system can cause preeclampsia and fetal loss.[53] Complement activation, likewise, is an important focus for lupus disease activity. While levels may be low in some patients with active SLE, complements can be unreliable as a biomarker of disease activity.[54] Finally, physiological maternal glucose alterations occur as the pregnancy progresses to deliver glucose to the fetus and support maternal metabolism. This diabetogenic state begins in the second trimester as maternal insulin resistance peaks in the third trimester.[55] Close monitoring of SLE patients who are on chronic corticosteroids is essential to evaluate for gestational diabetes. Below we discuss SLE patient monitoring by trimester (Table 3).

First Trimester

Common complaints in the first trimester of a normal pregnancy will include fatigue, weight gain, nausea, and urinary frequency. At each prenatal visit, the provider should complete a careful review of systems and physical exam with blood pressure monitoring for evidence of SLE disease activity. We recommend that patients do home blood pressure monitoring as well. Practitioners familiar with validated disease measurement tools (eg, systemic lupus erythematosus disease activity index (SLEDAI, British Isles Lupus Assessment Group (BILAG)) should consider incorporating these to assess disease activity. Laboratory assessments for medication toxicity and disease activity at least once a trimester should include: a complete blood count with differential, comprehensive metabolic panel, C3, C4, double-stranded DNA, serum uric acid, urinalysis with microscopy, and a urine protein to creatinine ratio (UPCR). All patients should be on

Table 3 Pregnancy Management

Timeline	Monitoring	Action Plan

Prenatal counseling	● Blood pressure check
	● SLE clinical assessments
	● Routine labs* with addition of anti-Ro/SSA, anti-La/SSB, antiphospholipid antibodies, lupus anticoagulant
		● If pregnancy is not desired, discuss effective birth control options
		● For those desiring pregnancy:
		  o Switch to pregnancy compatible medications
		  o Ensure low disease activity or remission at least 6 months
		  o Discontinue NSAIDS in those having difficulties conceiving
		  o Start on or continue with HCQ if not contraindicated

First Trimester	● Blood pressure check ● SLE clinical assessment ● Labs* ● Fetal ultrasound to ensure intrauterine pregnancy and establish gestational age	● Start Aspirin 81 mg/day ● Be vigilant for disease flares ● Review medication adherence ● Patients with OB-APS should start prophylactic heparin ● Patients with thrombotic APS should start full dose heparin ● for active SLE disease, increase or add pregnancy compatible DMARD
Second Trimester	● Blood pressure check ● SLE clinical assessment ● Labs* with assessment for gestational diabetes and genetic screening (if applicable) ● Fetal ECHO starting at week 16 through week 25 for mothers with +anti-Ro/SSA or +anti-La/SSB ● Ultrasound to evaluate fetal anatomy and to assess fetal growth, placental insufficiency	● Be vigilant for disease flares ● Review medication adherence ● In fetuses with evidence for 1st or 2nd degree heart block, start oral dexamethasone 4 mg daily for several weeks then assess response ● For fetuses with 3rd degree heart block without cardiac inflammation, avoid dexamethasone ● Avoid NSAIDS at 20 weeks and beyond.
Third Trimester	● Blood pressure check ● SLE clinical assessment ● Labs* ● Ultrasound regularly to evaluate fetal growth, adequacy of amniotic fluid, placental insufficiency	● Be vigilant for disease flares ● Review medication adherence ● Review preparations for labor and delivery
Post-partum and Lactation	● Blood pressure check ● SLE clinical assessment ● Labs*	● Be vigilant for disease flares ● Switch to lactation compatible medications if breastfeeding is desired ● For prednisone ≥20 mg/day, avoid breastfeeding 4 hours after dosing

Notes: *Labs to be included: complete blood count (CBC), comprehensive metabolic profile (CMP), urinalysis and morning urine protein to creatinine ratio (UPCR), anti-double stranded DNA (dsDNA) antibodies, complement levels (CH50, or C3 and C4), serum uric acid.
Abbreviations: SLE, systemic lupus erythematosus; HCQ, hydroxychloroquine; NSAIDS, nonsteroidal anti-inflammatory drugs; OB-APS, obstetric antiphospholipid syndrome; DMARD, disease modifying antirheumatic drug; ECHO, echocardiogram.

hydroxychloroquine (HCQ) unless contraindicated. Low dose aspirin (81mg/day) should be initiated early in pregnancy to reduce the risk for preeclampsia[56] In patients with known obstetric antiphospholipid syndrome (OB-APS), prophylactic heparin or low dose molecular weight heparin in combination with low dose aspirin is indicated to prevent fetal loss and thromboses; anticoagulation should be continued 6 to 12 weeks post-partum. Those patients with known thrombotic APS (T-APS) should receive therapeutic doses of heparin or low molecular weight heparin with low dose aspirin.[44] Frequency of follow-up will depend on the clinical status of the patient and at the provider's discretion. The provider and/or patient should inform their obstetrician of the pregnancy. Importantly, an early fetal ultrasound to confirm an intrauterine pregnancy and to establish fetal age is crucial.

Second Trimester

Anti-Ro/SSA (in particular, anti-Ro 52 or 60 kDa) and/or anti-La/SSB antibodies may cross the placenta in the second trimester and cause neonatal cutaneous lupus or CCHB.[57,58] Pregnant patients with these antibodies should undergo serial

fetal echocardiography by an experienced pediatric cardiologist or a maternal fetal medicine specialist starting at the 16th week of gestation to evaluate for cardiac conduction abnormalities as the vulnerable period is between 17 and 25 weeks gestation. First-, second-, and third-degree heart block may occur, but third-degree or CCHB is a permanent condition that carries significant morbidity and mortality; infants with CCHB often require permanent pacemakers.[57,58] In mothers who have had a previous infant with CCHB or cutaneous neonatal lupus, consider monitoring with weekly fetal echocardiography. When a fetus presents with first or second-degree heart block, the ACR Reproductive Health Guidelines conditionally recommends that the anti-Ro/SSA and/or anti-La/SSB mother take oral dexamethasone 4 mg daily for several weeks.[44] We do not recommend dexamethasone in situations of third degree heart block without evidence for cardiac inflammation as it does not reverse the conduction abnormality. In contrast to CCHB, cutaneous neonatal lupus is typically transient; affected infants may present with a rash, abnormal liver enzymes or hematologic abnormalities. Hydroxychloroquine continued during pregnancy will reduce the risk of CCHB and NLE.

Lupus flares may occur during pregnancy. For mild flares with arthralgias or myalgias, acetaminophen, topical pain creams and oral NSAIDs may be used, but at 20 weeks or later, nonsteroidal anti-inflammatory drugs (NSAIDS) should be discouraged. In instances where NSAIDS cannot be used or if the flare is more severe, pregnancy compatible disease modifying anti-rheumatic medications (DMARDS) should be added to hydroxychloroquine (see medications below). Keep prednisone at the lowest effective dose due to risk for mood changes, insomnia, infection, pregnancy-induced diabetes, macrosomia, adrenal insufficiency, and preterm delivery. During this trimester, it is necessary to remain vigilant for lupus disease activity that may not be clinically evident but can reveal itself on routine laboratory assessments. Continue to screen patients for evidence of active lupus nephritis, preeclampsia, and diabetes with blood work; assess fetal growth and anatomy, amniotic fluid level with fetal sonography. When there is a concern for placental integrity, fetal and uterine arteries with Doppler sonography should be performed.[56]

Third Trimester

Similar assessments should be conducted in the third trimester. Evaluate for pre-eclampsia or SLE flare regular or intrauterine growth restriction; Doppler sonography should continue at regular intervals. Mode and time of delivery will be determined by fetal and maternal conditions.

Postpartum

Mothers are at increased risk for thrombosis and disease flares during the postpartum period.[59] Those who have APS should remain on anticoagulation for at least 6–12 weeks after parturition.[56] Postpartum depression can be common and might be mistaken for neuropsychiatric lupus. Many medications used for SLE disease during pregnancy can be continued during lactation (see below). In mothers with anti-Ro/SSA or anti-La/SSB, observe for cutaneous lesions in the neonate; cutaneous NL may occur a few weeks after birth and can resolve spontaneously after weeks or months. These rashes are photosensitive; sun protection will help the rash resolve faster.[58]

Co-Existing Antiphospholipid Syndrome

Antiphospholipid syndrome (APS) is characterized as recurrent venous or arterial thromboses and pregnancy morbidity in the setting of aPL. About 29–46% of patients with SLE have evidence of aPL, but only 5–8% develop thrombotic or pregnancy complications (eg, fetal loss, preeclampsia/eclampsia, small for gestational age).[60,61] The revised classification criteria for APS defines vascular manifestations and obstetric complications; APS can occur by itself or in the setting of SLE. Thrombotic APS (T-APS) is defined by: one or more episodes of arterial, venous, or small vessel thrombosis in any tissue or organ, while obstetric APS is defined by: 1. three or more consecutive spontaneous abortions before 10 weeks of gestation, 2. one or more unexplained fetal loss beyond 10 weeks of gestation, or 3. one or more premature births of a morphologically normal neonate before 34 weeks of gestation due to eclampsia or preeclampsia.[62] The presence of aPL must occur on two or more occasions, separated by at least 12 weeks. Compared to other aPL, the lupus anticoagulant confers the highest risk for APO RR 12.15 (95% CI 2.92–50.54, p = 0.0006) Risk stratification and management of APS during pregnancy depends on prior thrombotic or obstetric complications.[44,56] The ACR Reproductive Health Guidelines indicate prophylactic therapy is not indicated

Table 4 Safety of Common SLE Treatments During Pregnancy and Lactation

Medication	Pre-Conception	During Pregnancy	Lactation
Compatible			
Hydroxychloroquine	+	+	+
Sulfasalazine	+	+	+
Azathioprine	+	+	+
Cyclosporine	+	+	+
Tacrolimus	+	+	+
Prednisone	Keep dose <20mg/day	Keep dose <20mg/d	Keep dose <20mg/d
NSAIDs	Discontinue w/difficulty conceiving	Stop at week 20	+
Stop at conception			
Belimumab	Stop with positive pregnancy test		+
Rituximab	Stop with positive pregnancy test		+
Abatacept	Stop with positive pregnancy test		+
Not compatible			
Cycophosphamide	Stop 3 mos before conception	X	x
MMF/mycophenolic acid	Stop 6 wks before conception	X	x
Leflunomide	Cholestyramine washout	X	x
Methotrexate	Stop 1 −3mos before conception	x	x- low transfer into breast milk

to prevent pregnancy loss for healthy, non-SLE patients with aPL but no prior history of thrombosis or pregnancy complications; however, aspirin 81–100 mg daily is conditionally recommended by the ACR Reproductive Health guidelines. We recommend, low dose aspirin with prophylactic doses of heparin (usually low molecular weight heparin) in women with obstetric APS. Continue anticoagulation for 6–12 weeks postpartum, as this is a vulnerable period for clotting. Pregnant women with T-APS should be prescribed aspirin and therapeutic dose heparin throughout pregnancy and postpartum. HCQ may help reduce the risk for thrombosis and APS-related poor outcomes. There is not enough evidence to show that prednisone, intravenous immunoglobulin, or higher doses of heparin will help APS-related outcomes.

Medications

Medication management during pregnancy must take into account any potential risk to the developing fetus (Table 4). Hydroxychloroquine is considered compatible with pregnancy.[44] Reassuringly, studies of neonates exposed to hydroxy-chloroquine in utero have not shown retinal toxicity or prolongation of neonatal QTc intervals.[63,64] Recently, there was a report of increased risk of fetal anomalies in infants exposed to hydroxychloroquine in utero; however, confounders such as alcohol, smoking, and other drugs were not assessed.[65] Importantly, no particular pattern of anomaly was found, the latter being a tenet of proof of teratogenicity.[66] Several studies have demonstrated that continuation of hydroxy-chloroquine during pregnancy decreases disease flares and reduces the risk of pre-eclampsia.[21] However, claims data demonstrate that overall 16.1% of women who have lupus are filling prescriptions during pregnancy.[67] Slightly higher results were found among those in Sweden, with 36% of SLE dispensed hydroxychloroquine during pregnancy.[68] Given this, we emphasize to our patients the importance of staying on hydroxychloroquine during pregnancy. This medication is also compatible with breastfeeding.[44]

Non-steroidal anti-inflammatory medications (NSAIDs) help control arthralgias and arthritis in SLE patients. The Food and Drug Administration (FDA) recently issued a warning that NSAIDS as a class may cause "rare but serious kidney problems in an unborn baby" that can lead to oligohydramnios and death around 20 weeks or later.[69] After 30 weeks of gestation, NSAIDs can cause premature closure of the ductus arteriosus.[44] We recommend that patients stop NSAIDs after week 20 of gestation. The exception to these recommendations is low dose aspirin that can be continued for the duration of the pregnancy. NSAIDs are compatible with breastfeeding.[44]

Early data suggested that glucocorticoids increased the risk for cleft palate formation.[70] However, in a large study from Denmark, increased rate of oral facial clefts were not found among 51,973 infants exposed to glucocorticoids in utero.[71] Nonetheless, glucocorticoids can contribute to gestational hypertension and diabetes, preterm premature rupture of the membranes and small for gestational age infants. Current recommendations advise keeping prednisone dose as low as possible during pregnancy. Similarly, in women on >20mg/d of prednisone, ACR guidelines suggest discarding breast milk for four hours following dosing.[44]

Sulfasalazine is sometimes used to control arthritis in SLE patients. Data gleaned from the inflammatory bowel disease literature supports its use during pregnancy.[72] There has been a case of diarrhea in a nursing child whose mother was taking sulfasalazine, so lactating women should consider discontinuing this medication if their infant develops diarrhea.[73]

Patients with significant organ involvement may require ongoing immunosuppression during pregnancy. Leflunomide, methotrexate and cyclophosphamide are either suspected or confirmed teratogenic medications and should be discontinued prior to conception. Leflunomide has a long half-life; women should undergo a drug elimination procedure with cholestyramine prior to conception; metabolite blood levels <0.03 µg/mL has been regarded as safe for pregnancy.[74] Methotrexate should be stopped one to three months prior to anticipated conception and cyclophosphamide treatment should be discontinued three months prior to conception.[44,55]

Mycophenolate mofetil/mycophenolic acid, are now the most commonly prescribed medication for lupus nephritis, is teratogenic and increases the risk for pregnancy loss in the first trimester.[75] A review of cumulative mycophenolate data in pregnancy showed the frequency of malformations is 22% and for spontaneous abortions to be 45%; inhibition of purine synthesis by mycophenolic acid is believed to be the cause of genotoxicity[76] Mycophenolate should be stopped six weeks respectively prior to conception.

Fortunately, azathioprine, cyclosporine and tacrolimus are compatible with pregnancy and can be substituted for the aforementioned potential teratogens.[44,55] The biologics rituximab, belimumab, and abatacept do not significantly cross the placenta until the 15th week of gestation; these medications can be continued through conception. In patients who are dependent on these biologics for disease control, discussing the potential risks of and benefits of these medications and through shared decision-making one can consider continuing these medications during pregnancy.

The Federal Drug Administration (FDA) recently approved voclosporin for the treatment of SLE nephritis; current recommendations are to avoid this medication in pregnant and lactating women.[77]

Treatment Approach

All women with SLE who are pregnant should continue hydroxychloroquine. Given the risk of pre-eclampsia, we recommend adding low dose aspirin at the end of the first trimester. Transition women who need ongoing immunosuppression for disease control to an immunosuppressive agent compatible with pregnancy (eg, tacrolimus, azathioprine or cyclosporine) and observe for four to six months to make certain that disease is stable prior to conception. For non-renal flares during pregnancy, treat with the lowest possible dose of prednisone. For renal flares, we recommend combination therapy of azathioprine with tacrolimus.

Many medications used for lupus management are compatible with lactation. Hydroxychloroquine, NSAIDs, sulfasalazine, and the immunosuppressive agents cyclosporine, azathioprine and tacrolimus are all compatible with breastfeeding. Biologics such as rituximab, and belimumab and likely abatacept are also compatible with lactation as these medications are all large molecules and do not readily get transferred into breast milk. Current recommendations are to avoid methotrexate in lactating women although there is growing evidence that little of this medication gets secreted in breast milk. Mycophenolate mofetil, cyclophosphamide and leflunomide should not be taken by lactating women.[44,55]

Conclusion

Systemic lupus erythematosus is a disease of reproductive aged women. Whereas formerly, providers counseled SLE patients to avoid pregnancy, improved disease management and a better understanding of medication safety render pregnancy a possibility for most SLE patients. Careful pregnancy planning for when disease is under good control with pregnancy compatible medications is crucial. Assembling a team that includes a maternal fetal medicine provider or

obstetrician who is familiar with caring for SLE patients is likewise important. All patients with SLE should remain on hydroxychloroquine during pregnancy unless contraindicated. We encourage patients at high risk for developing pre-eclampsia (older or younger age, primigravida, patients with hypertension, prior renal disease, presence of antiphospholipid antibodies) to initiate aspirin therapy (81mg/day) during the first trimester. Sulfasalazine, and the immunosuppressive agents cyclosporine, azathioprine, and tacrolimus are compatible with pregnancy. Rituximab, belimumab and other biologic agents can continue through conception. Glucocorticoids can help manage flares but providers should use the lowest dose possible for disease control. All of the aforementioned medications are compatible with breast- feeding. Cyclophosphamide, leflunomide, methotrexate, mycophenolate mofetil, and voclosporin should be stopped prior to pregnancy and avoided in lactating women. Women with anti-Ro and anti-La antibodies will need fetal screening for the development of congenital complete heart block. Successful pregnancies in patients with SLE are possible with close monitoring and a collaborative framework.

Disclosure

The authors report no conflicts of interest in this work.

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